Efavirenz (Sustiva, Stocrin)

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THE DETAILS

Brand Names:	Sustiva, Stocrin
Generic Name:	Efavirenz, EFV
Adult Single Dose:	One 600-mg tablet (once a day)
Food & Liquid Restrictions:	Take on an empty stomach, preferably at bedtime
Drug Class:	NNRTI

Truvada (Tenofovir/FTC)

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

Delavirdine (Rescriptor)
Efavirenz (Sustiva, Stocrin)
Nevirapine (Viramune)

Protease Inhibitors (PIs)

Amprenavir (Agenerase)
Atazanavir (Reyataz)
Fosamprenavir (908, Lexiva, Telzir)
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Taking Sustiva? Things You Should Know (Spring 1999)
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Sustiva Consumer Information (October 6, 1998)
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Pregnancy Risk Category Raised for Efavirenz (Summer 2005)
In *Bulletin of Experimental Treatments for AIDS*, from San Francisco AIDS Foundation

Efavirenz-Associated Neural Tube Defects Reported in Infants; Pregnancy Category Changed From C to D (March 31, 2005)
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Efavirenz, Stavudine Demand May Soon Exceed Supply in Developing World (March 4, 2005)
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Nelfinavir, Efavirenz, or Both After the Failure of Nucleoside Treatment of HIV Infection (August 9, 2001)
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PERSONAL ACCOUNTS

Life After Sustiva: Depression, Anxiety Side Effects (May/June 2004)
Gerry Hoyt is one of a small number of people who suffer severe, long-term psychological side effects while using efavirenz
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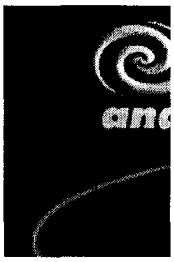

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A 4-drug Regimen Containing Sustiva (efavirenz) Plus Crixivan (indinavir) Results in a Superior Virologic Response and Less Toxicity Compared to a Regimen Containing Viracept (nelfinavir) Plus Indinavir

Combination antiretroviral regimens containing human immunodeficiency virus (HIV) type 1 protease inhibitors (PIs) provide clinical benefits and can achieve long-term virus suppression with partial reconstitution of the immunologic perturbations associated with HIV infection.

Although virologic response rates of 50%–90% have been described in some patient settings, patients with high HIV-1 RNA levels and low CD4 cell counts (advanced HIV disease) can have blunted responses to 3-drug regimens.

The optimal combination antiretroviral regimens for the treatment of advanced HIV disease have not been well defined. At the time of the design of this study, preliminary data suggested that regimens with 2 PIs might provide additional virological and pharmacological advantages in the treatment of HIV infection.

Previous data have suggested that nelfinavir, through its competitive inhibition of CYP3A4 activity, might allow for indinavir to be given every 12 h at a reduced dose of 1000 mg, providing an enhanced regimen that would facilitate the administration of indinavir. In addition, non nucleoside reverse-transcriptase inhibitors (NNRTIs) were recognized to be potent inhibitors of HIV-1 replication, and initial studies suggested that NNRTIs could enhance the efficacy of antiretroviral regimens.

On the basis of this information, in a randomized, open-label study, researchers evaluated 2 different 4-drug regimens containing indinavir with either efavirenz or nelfinavir for the treatment of patients with advanced HIV disease.

The 517 study subjects had no or limited previous experience with antiretroviral therapy. Subjects received Epivir (lamivudine) plus Retrovir (zidovudine) and Crixivan (indinavir) (**indinavir group**), Sustiva (efavirenz) plus indinavir (**efavirenz + indinavir group**), or Viracept (nelfinavir) plus indinavir (**nelfinavir + indinavir group**) and were monitored for 2.1 years.

Virologic failure was lower in the efavirenz + indinavir group ($P = .04$) and higher in the nelfinavir + indinavir group ($P = .006$), compared with that in the indinavir group.

No difference in grade 3 or 4 adverse event rates in the efavirenz + indinavir group ($P = .97$) and a trend toward an increased rate in the nelfinavir + indinavir group ($P = .07$), compared with the indinavir group, were noted.

A 4-drug regimen containing efavirenz plus indinavir resulted in a superior virologic response, whereas one containing nelfinavir plus indinavir resulted in an inferior response and a greater likelihood of toxicity.

Discussion

This study demonstrated that, in subjects with advanced HIV disease, treatment with a 4-drug regimen of efavirenz, indinavir, lamivudine, and zidovudine provided long-term virologic benefit, compared with a standard 3-drug regimen containing indinavir. A prolonged period of virus suppression characterized this superior response which resulted in a significant decrease in the risk for viral rebound.

This advantage occurred without adverse implications for toxicity or tolerability. A possible contributing factor to this observed virologic benefit is the sustained efavirenz plasma concentrations during long-term dosing. In treatment-naive subjects, the efavirenz inhibitory quotient (trough/IC_{50}) is high and sustained throughout the dosing interval, which may be beneficial when efavirenz is combined with a "nonboosted" PI, such as indinavir.

In contrast, the 4-drug regimen with nelfinavir, indinavir, lamivudine, and zidovudine did not provide additional virologic benefit, compared with the 3-drug regimen. An inferior short-term virologic response was observed, which was accompanied by a trend toward a greater likelihood of serious drug-associated toxicity.

The higher rate of adverse events observed in the nelfinavir + indinavir group may have contributed to the inferior response seen with this regimen. Similar findings have been noted in other studies evaluating 4-drug regimens

This study highlights the continued need for improved antiretroviral regimens for the treatment of HIV infection and the need for long-term studies, because the relative merits and toxicities of the studied regimens would not have been appreciated in a short-term study. The study further emphasizes the benefit of an efavirenz-based regimen as a strategy for increasing the potency of a regimen.

In contrast, the strategy of a dual-PI–based regimen with nelfinavir and indinavir was found not to be useful. The study also highlights the need to explore alternative strategies and emphasizes the need to balance the potency of regimens with their side effects. On the basis of these findings, more potent, but simplified, regimens should and are being explored.

09/05/03

Reference

MA Fischl and others. A Randomized Trial of 2 Different 4-Drug Antiretroviral Regimens versus a 3-Drug Regimen, in Advanced Human Immunodeficiency Virus Disease. *The Journal of Infectious Diseases* 188:625-634. September 1, 2003.

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AIDS INFONET • FACT SHEET 403

What Is Antiretroviral Therapy (ART)?

October 29, 2005

What Is ART?

ART means treating retroviral infections like HIV with drugs. The drugs do not kill the virus. However, they slow down the growth of the virus. When the virus is slowed down, so is HIV disease. Antiretroviral drugs are referred to as ARV. ARV therapy is referred to as ART.

What Is the HIV Life Cycle?

There are several steps in the HIV life cycle. (See Fact Sheet 106 for a diagram.)

1. Free virus circulates in the bloodstream.

2. HIV attaches to a cell.

3. HIV empties its contents into the cell (infects the cell).

4. The HIV genetic code (RNA) is changed into DNA by the reverse transcriptase enzyme.

5. The HIV DNA is built into the infected cell's DNA by the integrase enzyme.

6. When the infected cell reproduces, it activates the HIV DNA, which makes the raw material for new HIV viruses.

7. Packets of material for a new virus come together.

8. The immature virus pushes out of the infected cell in a process called "budding."

9. The immature virus breaks free of the infected cell.

10. The new virus matures: raw materials are cut by the protease enzyme and assembled into a functioning virus.

Approved ARV Drugs

Each type, or "class," of ARV drugs attacks HIV in a different way. The first class of anti-HIV drugs was the **nucleoside reverse transcriptase inhibitors**, also called "**nukes**." These drugs block Step 4, where the HIV genetic material is converted from RNA into DNA. Approved drugs in this class include:

- AZT (ZDV, zidovudine, Retrovir®)
- ddI (didanosine, Videx®)
- ddC (zalcitabine, Hivid®)
- d4T (stavudine, Zerit®)
- 3TC (lamivudine, Epivir®)
- Abacavir (Ziagen®)
- Tenofovir (Viread®) (a nucleotide)

- Combivir® (AZT/3TC combination)
- Trizivir® (AZT/3TC/Abacavir combination)
- Emtricitabine (FTC, Emtriva®)
- Truvada (combination of Emtriva and Viread)
- Epzicom (combination of abacavir and 3TC)

Another class of drugs blocks the same step of the life cycle, but in a different way. These are the **non-nucleoside reverse transcriptase inhibitors**, or **NNRTIs**. Three have been approved:

- Nevirapine (NVP, Viramune®)
- Delavirdine (DLV, Rescriptor®)
- Efavirenz (EFV, Sustiva®)

The third class of ARV drugs is the **protease inhibitors**. These drugs block Step 10, where the raw material for new HIV virus is cut into specific pieces. Ten protease inhibitors are approved:

- Saquinavir (SQV, Invirase® and Fortovase®)
- Indinavir (IDV, Crixivan®)
- Ritonavir (RTV, Norvir®)
- Nelfinavir (NFV, Viracept®)
- Amprenavir (APV, Agenerase®)
- Lopinavir (LPV, Kaletra®)
- Atazanavir (TAZ, Reyataz®)
- Fosamprenavir (908, Lexiva®)
- Tipranavir (PNU140690, Aptivus™)

The newest class of ARV drugs includes **fusion and attachment inhibitors**. They prevent HIV from attaching to a cell by blocking Step 2 of the life cycle. One fusion inhibitor has been approved:

- Enfuvirtide (Fuzeon® or T-20)

How Are the Drugs Used?

When HIV multiplies, most of the new copies are mutations: they are slightly different from the original virus. Some mutations keep multiplying even when you are taking an ARV drug. When this happens, the drug will stop working. This is called "developing resistance" to the drug.

If only one ARV drug is used, it is easy for the virus to develop resistance. But if two drugs are used, a successful mutant would have to "get around" both drugs at the same time. And if three drugs are used it's very hard for a mutation to show up that can resist all three drugs at the same time.

Using a triple-drug combination means that it takes much longer for resistance to develop. For this reason, using just one ARV drug (monotherapy) is not recommended.

Can These Drugs Cure AIDS?

A blood test called the "viral load" measures the amount of HIV virus in your bloodstream. People with lower viral loads stay healthier longer. See Fact Sheet 125 for more information on the viral load test.

Some people's viral load is so low that it is "undetectable" by the viral load test. This does **not** mean that all the virus is gone. Researchers used to believe that ARV therapy could eventually kill off all of the HIV virus in the body. Now this seems unlikely. The drugs do not "cure" AIDS. However, they make it possible for people with AIDS to live a long time.

When Do I Start?

There is not a clear answer to this question. Most doctors will consider three things: 1) your viral load; 2) your CD4 cell count; and 3) any symptoms you've had. ARV therapy is usually started if your viral load is over 100,000, if your CD4 cell count is below 350, or if you've had any symptoms of HIV disease. See Fact Sheet 404 for more information on treatment guidelines. This is an important decision you should discuss with your doctor.

Which Drugs Do I Use?

Each ARV drug has side effects. Some are serious. Refer to the fact sheet for each individual drug. Some combinations of drugs are easier to tolerate than others, and some seem to work better than others. Each person is different, and you and your doctor will have to decide which drugs to use.

The viral load test is now being used to see if ARV drugs are working. If the viral load does not go down, or if it goes down but comes back up, it might be time to change ARV drugs.

What's Next?

New drugs are being developed in all four of the existing classes. Researchers are also trying to develop new types of drugs, such as drugs that will block other steps in the HIV life cycle, and drugs that will strengthen the body's immune defenses. See Fact Sheets 460, 470 and 480 for more information on newer classes of drugs.

Our thanks to AIDS InfoNet, which provided this article to The Body.

TEST POSITIVE AWARE NETWORK

Sustiva Seems to Cause Prisoners to Wrongly Test Positive for Marijuana Use

By Enid Vázquez

November/December 2001

Inmate Efrain Campbell was eagerly looking forward to finishing his six months in solitary confinement following a fight at Illinois' Pontiac Correction Center (PCC). But then his drug tests kept coming back positive. He was accused of smoking marijuana and it was determined that he should be held another six months in solitary. At the same time, prisoner advocates learned that more than a dozen other prisoners at three different Illinois prisons were found to have "dirty drops" for marijuana, and were being punished by being put in solitary confinement or losing months of good time (which would have reduced their prison sentence). **One inmate lost six months of good time and six months of contact visits. Like Campbell, each prisoner was HIV-positive, and each was taking the anti-HIV drug Sustiva (efavirenz).**

Sustiva is known to make people wrongly test positive for marijuana use (called "false positive" results). But here the story gets tricky, and the crisis for the prisoners builds. (Remember when you see the word "assay" that it means a test.)

The Sustiva package insert is ambiguous: "False positive test results have only been observed with the CEDIA DAU Multi-Level THC assay, which is used for screening, and have not been observed with other cannabinoid assays tested, including tests used for confirmation of results." That makes it sound like Sustiva manufacturer DuPont Pharmaceuticals tested the med against all marijuana tests. In fact, the company did not do so, and it did not look at the test used in Illinois prisons, DrugCheck 5. DuPont only looked at three marijuana assays. The other two tests measured were Cannabinoid Enzyme Immunoassay from Diagnostic Reagents and AxSYM Cannabinoid assay from Abbott Laboratories.

This helps get the Illinois Department of Corrections (IDOC) off the hook for civil rights violations. In a letter to a prisoner advocate group, IDOC Deputy Chief of Institution Operations Larry Sims wrote that, "The Department is currently unaware of any scientific evidence to suggest that the DrugCheck 5 reacts to Sustiva by rendering a false positive. Research conducted by DuPont reflects that only the [CEDIA DAU] assay has been identified as creating false positives. Other assays do not cause false positives. The Department will continue to monitor this situation in an attempt to determine if a further investigation is warranted." But advocates say IDOC has done nothing.

In the midst of the Illinois crisis, the purchase of DuPont by Bristol-Myers Squibb was finalized on September 26. That left DuPont staff scrabbling, and allegedly unable to run lab tests to see how the Illinois marijuana test functions with Sustiva. But David Rosen, associate director of public affairs for DuPont Pharmaceuticals, said that the DrugCheck 5 package insert clearly states that a confirmatory test must be used and that it is up to IDOC to run those tests. He notes that even the CEDIA DAU test states that a confirmatory test must be given following positive results. The package insert for both tests states that, "The test provides only preliminary data which should be confirmed by other methods such as gas chromatography/mass spectrometry (GC/MS). Clinical consideration and professional judgment should be applied to any drug abuse test result particularly when preliminary positive results are used." Rosen also said it is up to the DrugCheck 5 manufacturer to test Sustiva for interactions. He said DuPont will look into changing the wording of its package insert, which requires approval by the Food and Drug Administration (FDA), and that such a change might be able to go into effect immediately.

In memos, prison healthcare providers reported simply that, "We have been directed from Office of Health Services that positive drug screens are a security issue, and we are not to get involved" and "Per the Office of Health Services, we can confirm for security you are on the medication but whether it causes false positive *is not a medical issue*." [Emphasis in the original.]

In a letter to IDOC director Donald N. Snyder, Jr., Charles A. Fasano, staff associate at the John Howard Association (a prison reform organization located in Chicago), explained that, "If use of a prescribed medication such as Sustiva, which is essential in AIDS treatment [as they are all], caused any false positive test results, inmates will be placed in a position of having to choose between punishment in segregation and prolonging their lives with a medication that leads to their placement in segregation." He adds that prisoners refuse to continue taking their Sustiva, "for fear that they will fail further random urine tests."

Prisoner advocate Dick Helms, also at the John Howard Association, says, "How can all of these people be flunking the test? That's too much of a coincidence." Prisoners taking Sustiva can contact Helms at the association, 300 W. Adams, Chicago, IL 60606; or Jackie Walker, National Prison Project, American Civil Liberties Union (ACLU), 733 15th St. NW, Suite 620, Washington, DC 20005. In the meantime, it is obvious that prisoners and others, such as people on methadone, need to reconsider going on Sustiva.

Got a comment on this article? Write to us at publications@tpan.com.

This article is a part of the publication *Positively Aware*.

Our thanks to Test Positive Aware Network, which provided this article to The Body.

PROJECT INFORM

What's New in Treatment Information?

Excerpts From Hotline Memos of March 2000 from the Information Department of Project Inform

April, 2000

Mouth Sores Study Enrolling

The National Institutes of Health (NIH) has asked us to share vitally important information for people with HIV or AIDS and mouth sores. Mouth sores can lead to serious problems: they can interfere with eating and can lead to poor nutrition and other serious health problems.

Doctors from the National Institutes of Dental and Craniofacial Research and the Clinical Center at NIH are looking for people over 17 years of age to take part in a study of a new treatment for mouth sores related to HIV and AIDS. Those who qualify for the study receive care by some of the nation's leading experts in the field.

The study medication, a thalidomide paste applied directly on the sores, is provided free. Patients can stay on their regular medical treatment for HIV or AIDS while participating in this study. NIH staff will accommodate flexible scheduling needs, as well as assist with transportation. The study takes place at the NIH Clinical Center in Bethesda, Maryland.

Patients or their doctors can contact the Principle Investigator of the study, Dr. Sharon Gordon, for more information:

Telephone: 1-888-606-0220
Fax: 301-496-1005
E-Mail: jbanks@dir.nidcr.nih.gov
Web: http://clinicalstudies.info.nih.gov

Hypersensitivity Reaction and Abacavir (Ziagen)

Glaxo Wellcome, the developers of abacavir (Ziagen), recently sent a letter to physicians alerting them of new symptoms in people who have hypersensitivity reactions to the drug. Previously the symptoms of the hypersensitivity reaction included fever, rash, nausea, vomiting, diarrhea, abdominal pain and fatigue.

More recently, several deaths have been reported in people with respiratory problems like shortness of breath (dyspnea), cough, or inflammation of the pharynx and who were later recognized with hypersensitivity reaction to abacavir. About 20% of people who initially experienced this hypersensitivity reaction had these respiratory symptoms.

The diagnosis of hypersensitivity reaction should be carefully considered for people with symptoms of respiratory diseases and other symptoms associated with hypersensitivity to abacavir, even if alternative respiratory diagnoses (pneumonia, bronchitis or flu-like illness) are possible. If the symptoms of the illness cannot be clearly differentiated from a hypersensitivity reaction, abacavir should be permanently discontinued. Abacavir should not be restarted following a hypersensitivity reaction because more severe symptoms will recur within hours and may include life-threatening hypotension (decrease in blood pressure) and death.

Efavirenz and Marijuana Tests

One complication of taking efavirenz (Sustiva) is that some people may have a false positive test for marijuana when drug-screening tests are used. These tests can detect chemicals found in marijuana that are released into urine. According to DuPont Pharmaceuticals, the manufacturer of efavirenz, a confirmatory test (using gas chromatography) will clear up the matter by revealing the presence of efavirenz and not the chemicals found in marijuana.

The wide scale availability of the genotypic resistance test has raised the issue about the proper interpretation of those results. Genotypic resistance examines samples of the virus from a person and looks for the presence of specific mutations that are known to be associated with resistance to certain drugs. Most reputable laboratories will include interpretation of the results, which is based on the most recent findings and usually developed with the help of a group of resistance experts not affiliated with the laboratory. Unfortunately there are also some laboratories that claim to offer expert interpretation of the results but have had a poor history of actually doing so. Some of the more reputable laboratories include:

- LabCorp/Virco
- Stanford
- Visible Genetics

First-Ever Testosterone-Replacement Gel Approved by FDA

AndroGel, a new testosterone-replacement therapy approach developed by Unimed Pharmaceuticals, Inc., has been approved by the Food and Drug Administration (FDA) for men with conditions associated with low testosterone levels.

AndroGel is a clear, colorless, topical (applied to the skin) gel that is applied once daily to shoulders, upper arms and/or abdomen (stomach area). It works similar to the testosterone patch. AndroGel has been shown to be effective in raising testosterone levels in men with low levels of this hormone. In one study, normal testosterone levels were reached within four hours of starting therapy. The gel appears to be able to sustain normal testosterone levels with continual use. (One study suggests that 87% of volunteers maintained testosterone levels within normal ranges through the last day of a 180-day treatment trial.)

AndroGel also appears to have the following beneficial effects associated with the biological function of testosterone:

- Increases total body and total body lean mass (muscle mass)
- Decreases total body fat
- Increases bone density
- Increases libido
- Positive effects on mood and fatigue

This gel can be applied at home, as opposed to injectable testosterone which sometimes requires doctor visits for injection, increasing ease of use for some people. It appears that AndroGel is absorbed into the skin well and quickly.

An interesting property of AndroGel is that, when treatment is stopped after achieving normal levels of testosterone, testosterone levels remain in the normal range for 24-48 hours (but return to pretreatment levels by the fifth day after the last application). This means that an individual may miss an occasional dose or two without compromising their therapy.

This therapy differs from other topical therapies (like "compounded" creams) because it is FDA-approved and applied only once a day. Compounded gels and creams have not been through thorough lab testing and must be applied twice a day. (A "compounded" cream is mixed up by a pharmacist who has special equipment.) Also, there may be some variability in the compounded creams you can get in pharmacies, and some doctors are unfamiliar with how to write prescriptions for compounded products. AndroGel may alleviate these problems by providing an alternative to compounded creams and gels.

Unfortunately, these characteristics of AndroGel may not make up for some of its significant shortcomings. Though Unimed claims that their product is better absorbed into the body than compounded creams and gels, research shows that they are generally absorbed to about the same extent. When this is compared to the relative price of each therapy option (estimated to be about $75/month for AndroGel and about $17/month for compounded creams and gels), the types of advantages that this product has over compounded creams

may not be worth the considerable price difference for many people.

Since skin remains exposed after AndroGel treatment, there are a few precautions that need to be taken for those using the therapy. First, people must be careful not to spread the gel from their hands or bodies to untreated individuals, especially women. (This is because women, when exposed to higher-than-normal levels of testosterone may develop secondary "male" characteristics including excessive facial and body hair.) Furthermore, extreme care should be made not to spread gel to pregnant women since testosterone is known to harm a developing fetus. Washing your hands after applying AndroGel and covering treated areas of the skin with clothing (once the gel has dried) will greatly reduce the likelihood of spreading the gel to another person.

Second, people may be forced to alter their lifestyle since they are advised to let the gel dry a few minutes before dressing and to wait five to six hours before showering or swimming so that it is properly absorbed. Another disadvantage is that gynecomastia (excessive development of the male breasts) frequently develops and occasionally persists during AndroGel therapy. In very rare cases, fluid build-up in certain tissues, possibly compounded with congestive heart failure, may be a serious complication in men with pre-existing heart, kidney, or liver conditions.

Also, AndroGel should be used with great caution among people who have one or more cancerous tumors in their breasts or have (or are suspected to have) one or more cancerous tumors in their prostate. Elderly men who use this gel may be at an increased risk for developing prostate cancer. AndroGel has not been adequately tested in women, but certainly women with cancer should use hormonal products with extreme care. However, the concerns about prostate and breast cancer apply to any therapy with any male sex hormone and are not entirely unique to AndroGel. AndroGel should be administered very cautiously if an individual also takes corticosteriods. Finally, AndroGel has not been studied, and thus not been approved for use, in men under 18 years of age. It has also not been well studied in women, though it is likely that women may consider using the product when appropriate.

AndroGel should be applied to clear, dry skin on the shoulders, upper arms, and/or abdomen once a day, preferably in the morning. AndroGel should not be applied to the genitalia. The recommended starting dose of AndroGel 1% is 5 G (to deliver 50 mg of testosterone). Blood testosterone levels should be measured approximately 14 days after starting therapy to make sure you have the proper dose. If the 5 G dose is too little, a 7.5 G and a 10 G dose are also available. AndroGel will be available in pharmacies around the middle of this year.

The most common immediate side effects (occurring in no more than 6% of the people studied) included: acne, application site reaction, headache, hypertension (high blood pressure), abnormal liver function tests, and non-cancerous prostate disorder. The most common long-term side effects (occurring in no more than 20% of people studied) included: abnormal liver function tests, acne, application site reaction, and prostate disorder (rarely cancerous).

The reported skin reactions at the application site were not severe enough to require treatment or stopping the drug. About 4% of people studied had reactions to AndroGel that required them to stop treatment.

What's New in Outreach?
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This article is a part of the publication *What's New?*.

Our thanks to Project Inform, which provided this article to The Body.

SUSTIVA®
(efavirenz) capsules and tablets
Rx only

DESCRIPTION

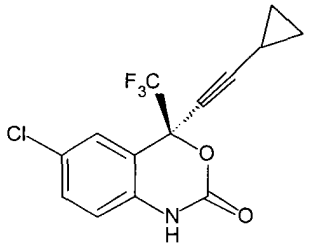
SUSTIVA (efavirenz) is an HIV-1 specific, non-nucleoside, reverse transcriptase inhibitor (NNRTI).

Capsules: SUSTIVA is available as capsules for oral administration containing either 50 mg, 100 mg, or 200 mg of efavirenz and the following inactive ingredients: lactose monohydrate, magnesium stearate, sodium lauryl sulfate, and sodium starch glycolate. The capsule shell contains the following inactive ingredients and dyes: gelatin, sodium lauryl sulfate, titanium dioxide and/or yellow iron oxide. The capsule shells may also contain silicon dioxide. The capsules are printed with ink containing carmine 40 blue, FD&C Blue No. 2 and titanium dioxide.

Tablets: SUSTIVA is available as film-coated tablets for oral administration containing 600 mg of efavirenz and the following inactive ingredients: croscarmellose sodium, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and sodium lauryl sulfate. The film coating contains Opadry® Yellow and Opadry® Clear. The tablets are polished with carnauba wax and printed with purple ink, Opacode® WB.

Efavirenz is chemically described as (S) -6- chloro-4-(cyclopropylethynyl)-1,4-dihydro-4-(trifluoromethyl)-2H-3,1-benzoxazin-2-one.

Its empirical formula is $C_{14}H_9ClF_3NO_2$ and its structural formula is:



Efavirenz is a white to slightly pink crystalline powder with a molecular mass of 315.68. It is practically insoluble in water (<10 µg/mL).

MICROBIOLOGY

Mechanism of Action: Efavirenz is a non-nucleoside reverse transcriptase (RT) inhibitor of human immunodeficiency virus type 1 (HIV-1). Efavirenz activity is mediated predominantly by non-competitive inhibition of HIV-1 RT. HIV-2 RT and human cellular DNA polymerases alpha, beta, gamma, and delta are not inhibited by efavirenz.

***In vitro* HIV Susceptibility:** The clinical significance of *in vitro* susceptibility of HIV-1 to efavirenz has not been established. The *in vitro* antiviral activity of efavirenz was assessed in lymphoblastoid cell lines, peripheral blood mononuclear cells (PBMCs) and macrophage/monocyte cultures. The 90-95% inhibitory concentration (IC_{90-95}) of efavirenz for wild type laboratory adapted strains and clinical isolates ranged from 1.7 to 25 nM. Efavirenz demonstrated synergistic activity against HIV-1 in cell culture when combined with zidovudine (ZDV), didanosine, or indinavir (IDV).

Resistance: HIV-1 isolates with reduced susceptibility to efavirenz (>380-fold increase in IC_{90}) compared to baseline can emerge *in vitro*. Phenotypic (N=26) changes in evaluable HIV-1 isolates and genotypic (N=104) changes in plasma virus from selected patients treated with efavirenz in combination with IDV, or with ZDV plus lamivudine were monitored. One or more RT mutations at amino acid positions 98, 100, 101, 103, 106, 108, 188, 190 and 225, were observed in 102 of 104 patients with a frequency of at least 9% compared to baseline. The mutation at RT amino acid position 103 (lysine to asparagine) was the most frequently observed (≥90%). A mean loss in susceptibility (IC_{90}) to efavirenz of 47-fold was observed in 26 clinical isolates. Five clinical isolates were evaluated for both genotypic and phenotypic changes from baseline. Decreases in efavirenz susceptibility (range from 9 to >312-fold increase in IC_{90}) were observed for these isolates *in vitro* compared to baseline. All 5 isolates possessed at least one of the efavirenz-associated RT mutations. The clinical relevance of phenotypic and genotypic changes associated with efavirenz therapy is under evaluation.

Cross-Resistance: Rapid emergence of HIV-1 strains that are cross-resistant to non-nucleoside RT inhibitors has been observed *in vitro*. Thirteen clinical isolates previously characterized as efavirenz-resistant were also phenotypically resistant to nevirapine and delavirdine *in vitro* compared to baseline. Clinically derived ZDV-resistant HIV-1 isolates tested *in vitro* retained susceptibility to efavirenz. Cross-resistance between efavirenz and HIV protease inhibitors is unlikely because of the different enzyme targets involved.

CLINICAL PHARMACOLOGY

Pharmacokinetics

Absorption: Peak efavirenz plasma concentrations of 1.6-9.1 μM were attained by 5 hours following single oral doses of 100 mg to 1600 mg administered to uninfected volunteers. Dose-related increases in C_{max} and AUC were seen for doses up to 1600 mg; the increases were less than proportional suggesting diminished absorption at higher doses.

In HIV-infected patients at steady-state, mean C_{max}, mean C_{min}, and mean AUC were dose proportional following 200 mg, 400 mg, and 600 mg daily doses. Time-to-peak plasma concentrations were approximately 3-5 hours and steady-state plasma concentrations were reached in 6-10 days. In 35 patients receiving SUSTIVA 600 mg once daily, steady-state C_{max} was 12.9 ± 3.7 μM (mean ± S.D.), steady-state C_{min} was 5.6 ± 3.2 μM, and AUC was 184 ± 73 μM•h.

Effect of Food on Oral Absorption:
Capsules – Administration of a single 600-mg dose of efavirenz capsules with a high fat/high caloric meal (894 kcal, 54 g fat, 54% calories from fat) or a reduced fat/normal caloric meal (440 kcal, 2 g fat, 4% calories from fat) was associated with a mean increase of 22% and 17% in efavirenz AUC∞ and a mean increase of 39% and 51% in efavirenz C_{max}, respectively, relative to the exposures achieved when given under fasted conditions. (See **DOSAGE AND ADMINISTRATION** and **PRECAUTIONS; Information for Patients**.)

Tablets – Administration of a single 600-mg efavirenz tablet with a high fat/high caloric meal (approximately 1000 kcal, 500-600 kcal from fat) was associated with a 28% increase in mean AUC∞ of efavirenz and a 79% increase in mean C_{max} of efavirenz relative to the exposures achieved under fasted conditions. (See **DOSAGE AND ADMINISTRATION** and **PRECAUTIONS; Information for Patients**.)

Distribution: Efavirenz is highly bound (approximately 99.5-99.75%) to human plasma proteins, predominantly albumin. In HIV-1 infected patients (N=9) who received SUSTIVA 200 to 600 mg once daily for at least one month, cerebrospinal fluid concentrations ranged from 0.26 to 1.19% (mean 0.69%) of the corresponding plasma concentration. This proportion is approximately 3-fold higher than the non-protein-bound (free) fraction of efavirenz in plasma.

Metabolism: Studies in humans and *in vitro* studies using human liver microsomes have demonstrated that efavirenz is principally metabolized by the cytochrome P450 system to hydroxylated metabolites with